Prevalence and Determinants of Valvulopathy in Patients Treated With Dexfenfluramine

Bruce K. Shively, MD; Carlos A. Roldan, MD; Edward A. Gill, MD; Thomas Najarian, MD; Sonja Barton Loar, PharmD

Background—Valve regurgitation has been associated with dexfenfluramine, but its prevalence and severity are uncertain. Additional factors that may contribute to valve regurgitation in patients exposed to this drug are poorly understood.

Methods and Results—Echocardiography was performed on subjects recruited from 26 prescribing sites in 15 states. The total sample of 412 subjects included 172 dexfenfluramine patients and 172 unexposed controls matched for age, sex, and body mass index and 68 unmatched subjects meeting the same entry criteria (51 dexfenfluramine patients and 17 controls). Mean treatment duration was 6.9 months; mean interval from treatment discontinuation to echocardiogram was 8.5 months. Each echocardiogram was interpreted independently by 3 echocardiographers. FDA-grade regurgitation (at least mild aortic regurgitation or at least moderate mitral regurgitation) was significantly more frequent in dexfenfluramine patients (7.6% versus 2.1% for controls; \( P=0.01 \); odds ratio, 3.82). This difference was primarily due to more frequent mild aortic regurgitation in dexfenfluramine patients (6.3% versus 1.6% in controls; \( P<0.02 \); odds ratio, 4.15). No differences were found in sclerosis or mobility for either the aortic or mitral valve. Factors independently related to FDA-grade regurgitation or any grade of aortic regurgitation were older age, higher diastolic blood pressure at the time of echocardiography, and shorter time from drug discontinuation to echocardiogram.

Conclusions—Dexfenfluramine use is associated with an increase in the prevalence of abnormal valve regurgitation. Age and blood pressure may also affect the prevalence of regurgitation. Dexfenfluramine-related valve regurgitation may regress after drug discontinuation.

Key Words: dexfenfluramine • drugs • echocardiography • regurgitation • valves

Dexfenfluramine and the combination of fenfluramine and phentermine may be associated with valve disease. On the basis of data that showed a prevalence of abnormal valve regurgitation of \( \sim 30\% \) in 291 patients treated with dexfenfluramine, dexfenfluramine-phentermine, or fenfluramine-phentermine versus 2.1% in historical controls, fenfluramine and dexfenfluramine were withdrawn from the market in September 1997. Subsequent reports have supported an association between dexfenfluramine use and valve regurgitation, but estimates of regurgitation prevalence and severity vary. Khan et al found a prevalence of FDA-grade regurgitation (at least mild aortic regurgitation or at least moderate mitral regurgitation) of 17% in 70 dexfenfluramine patients versus 1.3% in 233 controls (\( P<0.01 \)), whereas Weissman et al showed a prevalence of 6.9% in 718 dexfenfluramine patients versus 4.5% in 354 controls (\( P=\text{NS} \)). Interpretation of these results is confounded by methodological differences between the studies, such as concomitant treatment with phentermine, variable duration of treatment, prior treatment with other anorexigens, and non-blinded performance or interpretation of echocardiograms. As a result, the prevalence and severity of valve regurgitation associated with dexfenfluramine remain uncertain.

Increased dosage and duration of therapy may increase the risk of valve regurgitation as a result of anorexigens. Conversely, if the valvulopathy is reversible, a longer time interval from drug discontinuation to echocardiography may lead to a lower regurgitation prevalence. Other potential codeterminants include age, diabetes, and hypertension. Because serotonin has been implicated in the pathogenesis of valve injury due to these drugs, concomitant treatment with medications that exhibit monoamine oxidase inhibitory activity, which could increase platelet or blood serotonin levels, may be important.

To establish the prevalence of valve disease in a representative sample of dexfenfluramine patients and to investigate the role of contributing factors, we performed an echocardiographic follow-up prevalence study of dexfenfluramine patients and matched controls.
Methods

Patients

Patients were enrolled from 26 prescribing sites in 15 states. Sites were selected from a list of prescribers of dexfenfluramine provided by Interneuron Pharmaceuticals, Inc. Selection was based on the ability of the site to identify a minimum of 5 patients treated with only dexfenfluramine and 5 potential controls for each patient that met the criteria specified below. Each site was required to provide complete demographic, medical history, and physical examination data on patients and controls. Approval for the use of human subjects at each site was obtained through a local or a central Institutional Review Board. All subjects gave written informed consent.

Entry criteria for dexfenfluramine-treated patients were as follows: age ≥18 years; last prescribed dose no earlier than June 30, 1997; treatment for ≥3 continuous months; and no other anorexigens or serotonergic drugs within the preceding 5 years. For the present study, anorexigens included fenfluramine, phentermine, any “herbal phen-fen” products, and St John’s wort, and serotonergic drugs included ergot alkaloids, sumatriptan, and methysergide.

Controls were selected from obese patients seen at the same prescribing site who also had not taken these medications for the preceding 5 years. Controls (n=3) were computer-matched to each dexfenfluramine patient by sex, age (within 5 years), and body mass index (within 4 kg/m²). The controls were invited to participate in random order; the first control to consent was used for the final match.

In addition to 172 patient-control pairs, the total sample included an unpaired sample of 68 subjects who met the same entry criteria as the paired sample. For these subjects, either the paired subject’s echocardiogram was not performed (39 patients, 8 controls) or an error in matching was discovered after the echocardiogram was obtained (12 patients and 9 controls). Other errors identified by quality control measures after echocardiography were 1 control who had prior treatment with fenfluramine-phentermine, 12 subjects who previously had taken other anorexigens (none associated with valve disease to date), and 17 patients who had dexfenfluramine treatment for <3 months.

Clinical Data

Subjects were not excluded for a history of cardiovascular disorders, prior valve disease, or murmur. A list of medications taken since June 15, 1996, was recorded. Dosage of dexfenfluramine was not recorded; 86% of dexfenfluramine prescriptions were written for 15 mg BID during the period of US drug approval, April 1996 to September 1997 (IMS America, unpublished data, 1997).

Echocardiography

An echocardiographic laboratory near each prescribing site was evaluated for ability to perform the required echocardiographic protocol by submission of a test study. Echocardiography laboratories were blinded to patient treatment status; patients and technicians were instructed not to discuss patient medication history.

The Doppler echocardiographic examination protocol developed for the present study included a complete standard Doppler echocardiogram with supplemental parasternal views in the long and short axis of each valve to take advantage of transducer proximity to the valves and multiple “zoom” images. M-mode recordings were made of both mitral valve leaflets, 2 or 3 aortic cusps (in the parasternal short axis), the septal and anterolateral tricuspid leaflets, and the medial pulmonary valve cusp. All valves were examined by color Doppler in multiple views; regurgitation was confirmed by pulsed or continuous-wave Doppler.

Each echocardiogram was interpreted independently with prescribed criteria by 3 experienced echocardiographers at 3 institutions (B.K.S., C.A.R., and E.A.G.). Regurgitation of 1+ degree (“trace”) was defined as a small jet (usually <1 cm in length) visualized in ≥2 consecutive color Doppler frames. Usually 1+ degree regurgitation was limited to the beginning of the regurgitation period. Aortic regurgitation of 2+ degree (“mild”) was defined as a jet occupying <25% of the left ventricular outflow tract diameter.

The pressure half-time, if determinable, was >400 ms. Mitral regurgitation of 2+ degree was defined as a color Doppler jet extending 2 to 5 cm into the left atrium and occupying ≤25% of the left atrial area in the 4-chamber view. Mitral regurgitation of 3+ degree was defined as a jet >4 cm in length and occupying 25% to 50% of the left atrial area. Aortic regurgitation of ≥3+ and 4+ mitral regurgitation were not found in any subject. Grading criteria for tricuspid regurgitation were similar to those for mitral regurgitation. Pulmonary regurgitation was graded 1+, 2+, or 2+ according to jet length of ≥1 cm or 1 to 3 cm, respectively. No instances of ≥2+ pulmonary regurgitation were encountered.

Valves and associated structures were rated for sclerosis, defined as increased apparent thickness and reflectance, on a 0 to 4+ scale for which 0 was normal; 1+, slight sclerosis (barely discernible as abnormal); 2+, a mild increase in thickness and reflectance; 3+, moderate sclerosis; and 4+, severe sclerosis. Ratings on a similar 0 to 4+ scale were also performed for mobility of the anterior and posterior leaflets of the mitral valve and each cusp of the aortic valve.

Differences in ratings among the 3 readers were resolved as follows. If 1 reader differed from the other 2 by 1 grade, the majority rating was assigned. If each reader gave a different rating or if any rating differed from another by >1 grade, the echocardiogram was reread and a final rating assigned by the lead echocardiographer (B.K.S.).

In a random sample of 35 dexfenfluramine patients and 35 controls, mobility of the mitral valve posterior leaflet was quantified as the angle of maximal opening in the 2D parasternal long-axis view. At the E point, this angle was defined as the angle formed by lines connecting the tip of the posterior leaflet, the base of the posterior leaflet (the vertex of the angle), and the base of the anterior leaflet. Similarly, the mobility of the anterior leaflet was quantified as the angle formed by lines connecting the tip of the anterior leaflet, the base of the anterior leaflet (the vertex of the angle), and the base of the posterior leaflet. A smaller maximum angle of opening indicates reduced leaflet mobility. Aortic valve mobility was quantified on M-mode in the parasternal long-axis view as an index equal to the difference between the aortic annular diameter and the mean of the separation of the right and noncoronary cusps and the separation of the right and left coronary cusps. A larger value of this index indicates reduced mobility.

In a different random sample, pulmonary artery systolic pressure was estimated in 35 dexfenfluramine patients and 35 controls. Echocardiograms were rated for image quality by the lead echocardiographer as follows: A, excellent or good, equivalent to the upper 60% of studies seen in clinical practice, or B, fair or poor.

Statistical Analysis

Regurgitation frequencies in the dexfenfluramine and control groups were analyzed according to grade of severity (ie, 1 to 4+) and regurgitation of any grade (present or absent) and of FDA grade (at least moderate mitral regurgitation or at least mild aortic regurgitation). In addition, the prevalence of FDA-grade regurgitation of either the mitral or aortic valve was assessed. For the total sample, the significance of differences in regurgitation prevalence between patients and controls was tested by χ² or Fisher’s Exact test. The occurrence of discordance in the presence of regurgitation between dexfenfluramine patients and controls in the paired sample was tested for significance by McNemar’s test. The 95% confidence limits for the odds ratios (ORs) were calculated using large-sample normal approximations. All other analyses were performed on the total sample. Differences in valve sclerosis, mobility, and estimated pulmonary systolic pressure were analyzed using χ² and Student’s t test.

The influence of other variables on the prevalence of valve regurgitation of any grade and of FDA grade in the dexfenfluramine and control groups was assessed with Fisher’s Exact or χ² test for dichotomous variables and logistic regression analysis for scalar and continuous variables. Variables assessed were age, sex, body mass index, blood pressure immediately after echocardiogram (diastolic and systolic), diabetes, history of hypertension, duration of dexfen-
Valvulopathy With Dexfenfluramine

Results

Pertinent characteristics of the paired, unpaired, and total samples are shown in Table 1. The subjects were predominantly moderately obese white women (mean age, 50 years). Hypertension and diabetes were common in both dexfenfluramine patients and controls. Mean treatment duration was 6.9 months (range, 0.5 to 17.0 months) in the total dexfenfluramine sample and 7.0 months (range, 1.6 to 17.0 months) in the paired sample. The mean interval from discontinuation of treatment to echocardiography was 8.5 months (range, 3.2 to 17.0 months) in the total dexfenfluramine sample and 7.0 months (range, 1.6 to 17.0 months) in the paired sample. The mean interval from discontinuation to echocardiogram, concomitant treatment with medication classified as possessing monoamine oxidase inhibitory activity (see Appendix A) and echocardiogram quality. Date of treatment discontinuation was obtained by history from dexfenfluramine patients to assess the effect of time from drug discontinuation to echocardiography on regurgitation. For scalar and continuous variables found to be significant in the univariate analyses, a value of 0.05 was considered significant. Multiple logistic regression analysis was performed for FDA-grade regurgitation and any aortic regurgitation using variables found to be significant in the univariate analyses. A value of $P<0.05$ was considered significant. Multiple logistic regression analysis was performed for FDA-grade regurgitation and any aortic regurgitation using variables found to be significant in the univariate analyses. A value of $P<0.05$ was considered significant. Multiple logistic regression analysis was performed for FDA-grade regurgitation and any aortic regurgitation using variables found to be significant in the univariate analyses. A value of $P=0.15$ ($\chi^2$ increment of 2.07) was used as the cutoff for inclusion in the models. The percentage of concordance between each possible pair of interpreters for all 412 echocardiograms was calculated.

Valve Regurgitation and Dexfenfluramine

No instances existed of severe (4+) mitral regurgitation. FDA-grade mitral regurgitation (moderate or 3+) was infrequent among dexfenfluramine patients and controls (total sample, 1.3% and 0.5%, respectively) (Figure 1). In both the total and paired samples, no significant differences were seen between the dexfenfluramine and control groups in the prevalence of FDA-grade mitral regurgitation, each individual grade of mitral regurgitation, or the presence of any mitral regurgitation. Aortic regurgitation of either 3+ or 4+ severity was not found. In the total and paired samples, significantly more FDA-grade (mild or 2+) aortic regurgitation was seen in dexfenfluramine patients (total sample, 6.3% versus 1.6% in controls; $P<0.02$; OR, 4.15; 95% CI, 1.18 to 14.7; paired sample, 6.4% versus 1.7% in controls; $P<0.04$; OR, 3.85; 95% CI, 1.05 to 14.05). Also, more aortic regurgitation of any grade was found in dexfenfluramine patients (total sample, 21.5% versus 11.1% in controls; $P=0.005$; OR, 2.19; 95% CI, 1.26 to 3.82; paired sample, 22.1% versus 11.6% in controls; $P=0.01$; OR, 2.16; 95% CI, 1.20 to 3.89) (Figure 2). FDA regurgitation of either valve was also more frequent in the dexfenfluramine patients (total sample, 7.6% versus 2.1%; $P=0.01$; OR, 3.82; 95% CI, 1.26 to 11.55; paired sample, 7.6% versus 2.3% in controls; $P=0.03$; OR, 3.43; 95% CI, 1.10 to 10.75). Analysis of discordance within pairs of the paired sample confirmed these differences (Figure 3). No differences existed in the prevalences of tricuspid or pulmonary regurgitation between the groups.

Valve Sclerosis, Mobility, and Other Echocardiographic Data

No differences were seen between dexfenfluramine patients and controls in the frequencies of sclerosis or in valve mobility. The aortic cusp mobility index was 0.22 cm for dexfenfluramine patients and 0.20 cm for controls ($P<0.02$; OR, 4.15; 95% CI, 1.18 to 14.7; paired sample, 6.4% versus 1.7% in controls; $P<0.04$; OR, 3.85; 95% CI, 1.05 to 14.05). Also, more aortic regurgitation of any grade was found in dexfenfluramine patients (total sample, 21.5% versus 11.1% in controls; $P=0.005$; OR, 2.19; 95% CI, 1.26 to 3.82; paired sample, 22.1% versus 11.6% in controls; $P=0.01$; OR, 2.16; 95% CI, 1.20 to 3.89) (Figure 2). FDA regurgitation of either valve was also more frequent in the dexfenfluramine patients (total sample, 7.6% versus 2.1%; $P=0.01$; OR, 3.82; 95% CI, 1.26 to 11.55; paired sample, 7.6% versus 2.3% in controls; $P=0.03$; OR, 3.43; 95% CI, 1.10 to 10.75). Analysis of discordance within pairs of the paired sample confirmed these differences (Figure 3). No differences existed in the prevalences of tricuspid or pulmonary regurgitation between the groups.

![Figure 1. Prevalence of mitral regurgitation (MR) of each grade in the dexfenfluramine patients (Dexfen) vs controls (total sample). No significant differences were found between the 2 groups.](http://circ.ahajournals.org/doi/abs/10.1161/CIRCULATIONAHA.117.028487)

<table>
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<tr>
<td>Diabetes, %</td>
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<tr>
<td>Treatment duration, mo</td>
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<tr>
<td>End of treatment-echocardiogram, mo</td>
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</tbody>
</table>

Data presented are No. of patients or mean±SD unless otherwise specified. BMI indicates body mass index; Dexfen, dexfenfluramine treatment.

Valve Sclerosis, Mobility, and Other Echocardiographic Data

No differences were seen between dexfenfluramine patients and controls in the frequencies of sclerosis or in valve mobility. The aortic cusp mobility index was 0.22 cm for dexfenfluramine patients and 0.20 cm for controls ($P<0.02$; OR, 4.15; 95% CI, 1.18 to 14.7; paired sample, 6.4% versus 1.7% in controls; $P<0.04$; OR, 3.85; 95% CI, 1.05 to 14.05). Also, more aortic regurgitation of any grade was found in dexfenfluramine patients (total sample, 21.5% versus 11.1% in controls; $P=0.005$; OR, 2.19; 95% CI, 1.26 to 3.82; paired sample, 22.1% versus 11.6% in controls; $P=0.01$; OR, 2.16; 95% CI, 1.20 to 3.89) (Figure 2). FDA regurgitation of either valve was also more frequent in the dexfenfluramine patients (total sample, 7.6% versus 2.1%; $P=0.01$; OR, 3.82; 95% CI, 1.26 to 11.55; paired sample, 7.6% versus 2.3% in controls; $P=0.03$; OR, 3.43; 95% CI, 1.10 to 10.75). Analysis of discordance within pairs of the paired sample confirmed these differences (Figure 3). No differences existed in the prevalences of tricuspid or pulmonary regurgitation between the groups.

Valve Sclerosis, Mobility, and Other Echocardiographic Data

No differences were seen between dexfenfluramine patients and controls in the frequencies of sclerosis or in valve mobility. The aortic cusp mobility index was 0.22 cm for dexfenfluramine patients and 0.20 cm for controls ($P=NS$). The mitral leaflet angles of maximum opening for dexfenfluramine patients and controls were 84.3° and 84.2°, respectively, for the anterior leaflet ($P=NS$) and 75.8° and 77.1° for the posterior leaflet ($P=NS$).

Valve Sclerosis, Mobility, and Other Echocardiographic Data

No differences were seen between dexfenfluramine patients and controls in the frequencies of sclerosis or in valve mobility. The aortic cusp mobility index was 0.22 cm for dexfenfluramine patients and 0.20 cm for controls ($P=NS$). The mitral leaflet angles of maximum opening for dexfenfluramine patients and controls were 84.3° and 84.2°, respectively, for the anterior leaflet ($P=NS$) and 75.8° and 77.1° for the posterior leaflet ($P=NS$).
the posterior leaflet ($P=\text{NS}$). Estimated pulmonary artery pressure was normal in both groups (26.7 mm Hg in dexfenfluramine patients versus 25.6 in controls, $P=\text{NS}$).

Other Factors Related to Valve Regurgitation

Several factors in addition to dexfenfluramine treatment were related to either the presence of any grade of aortic regurgitation or FDA-grade regurgitation of either valve. Age was associated with increased FDA-grade regurgitation in control subjects (9.5% of those $\geq$60 years old versus none of those <60; $P<0.001$) but not in the dexfenfluramine patients. Increased diastolic blood pressure at the time of echocardiography was associated with more frequent aortic regurgitation and FDA-grade regurgitation of either valve. This effect was strongest for any grade of aortic regurgitation in dexfenfluramine patients and was not significant in controls (Figure 4). The OR of any aortic regurgitation was 1.052/mm Hg in the dexfenfluramine group ($P=0.0015$; 95% CI, 1.019 to 1.087) versus 0.967 ($P=0.12$ for an association in the opposite direction; 95% CI, 0.926 to 1.009) in the control group. The prevalence of any degree of aortic regurgitation was significantly higher in dexfenfluramine patients only, those treated with medications with monoamine oxidase inhibitory activity showed a trend toward more frequent FDA-grade regurgitation compared with those not treated with such medications (11.3% versus 4.8%; $P=0.07$). Duration of dexfenfluramine treatment was not related to valve regurgitation in the present study.

Multivariate Analysis of Valve Regurgitation

The results of logistic regression analysis of the factors related to valve regurgitation are shown in Table 2. Analyses were performed for any grade of aortic regurgitation and FDA-grade regurgitation of either valve. Factors independently contributing to any aortic regurgitation were as follows: dexfenfluramine treatment, diastolic blood pressure at the time of echocardiography, and echocardiogram quality. Factors independently related to FDA regurgitation of either valve were: dexfenfluramine treatment, age, and diastolic blood pressure. In dexfenfluramine patients only, diastolic blood pressure and treatment with a monoamine oxidase inhibiting medication were independently related to FDA-grade regurgitation.

Interobserver Variability

Table 3 shows the percentage agreement and $\kappa$ value for each possible pairing of echocardiographic raters for 6 important variables on the total sample ($n=412$). For most variables, $\geq85\%$ of all ratings were of the same grade and $>95\%$ of all ratings were within 1 grade of each other.

Discussion

In the present study, FDA-grade regurgitation was significantly more prevalent in dexfenfluramine-treated obese patients (7.6%) than in controls (2.1%). This difference was also significant in the analysis of patient-control matched pairs. The dexfenfluramine patients differed from controls primarily in the frequencies of trace and mild aortic regurgitation.

![Figure 2](image2.png)

**Figure 2.** Prevalence of aortic regurgitation (AR) and FDA-grade regurgitation of either valve in the dexfenfluramine patients (Dexfen) vs controls (total sample). *$P<0.02$; **$P=0.01$; and ***$P=0.005$.

![Figure 3](image3.png)

**Figure 3.** Frequencies of concordance and discordance of matched pairs for presence of valve regurgitation. Abbreviations are as in Figures 1 and 2.

![Figure 4](image4.png)

**Figure 4.** Effect of progressively higher diastolic blood pressure on frequency of aortic regurgitation of any degree in dexfenfluramine patients vs controls. For dexfenfluramine patients, $P=0.03$ by Mantel-Haenszel test; for controls, $P=\text{NS}$.
After a mean of 6.9 months of dexfenfluramine therapy in 223 patients, with echocardiograms performed a mean of 8.5 months after drug discontinuation, no instances of severe regurgitation or of moderate aortic regurgitation were encountered and moderate mitral regurgitation was present in 1.3% of patients.

Several important methodological differences exist between the present study and those previously reported. Treatment with dexfenfluramine alone was noted in 15 of the 284 patients reported by the FDA, but the results for these patients were not presented separately, and the OR of 14.6 for FDA-grade regurgitation includes additional patients that received combined treatment with phentermine.4 Weissman et al5 studied dexfenfluramine alone and reported an OR of 1.6 (95% CI 0.9 to 2.8). Khan et al8 reported an OR of 12.7 (2.9 to 56.4) for dexfenfluramine alone, which was less than that for dexfenfluramine-phentermine (OR, 24.5, 5.9 to 102.2).

Shorter exposure to dexfenfluramine in the study of Weissman et al5 may contribute to the comparatively low OR (mean, 2.4 months). However, dexfenfluramine treatment duration was also short in the study of Khan et al8 (mean, 4.9 months versus 6.9 months in the present study). Treatment duration may have been longer in the FDA report (overall median, 14 months), but specific duration data for dexfenfluramine are not given.4 For comparison, a medical reimbursement database of 13 718 dexfenfluramine patients in the United States shows that 84% were treated for ≤4 months, and ≤9.1% took phentermine concurrently (IMS America, unpublished data, 1998).

The possibility of regression of valvulopathy has been raised in several abstracts and a case report.12 The interval from drug discontinuation to echocardiography was longer in the present study (mean, 8.5 months) than in those of Weissman et al5 (mean of 1.3 months), Khan et al8 (38% <1 month, 30% 1 to 6 months, 32% >6 months), and probably the FDA.4 Regression of valvulopathy could account for the lesser effect of dexfenfluramine found in the present study compared with the reports by Khan et al and the FDA. This possibility is supported by the finding of less regurgitation after an 8-month interval in the present study.

Other factors in addition to dexfenfluramine were found to have a significant effect on the prevalence of valve regurgitation in the present study. A higher prevalence of minor valve regurgitation in older persons has been shown in previous population-based studies14,15 and in the study of Khan et al8. Age emerged in the present study as an independent predictor of FDA-grade regurgitation, even

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MAOI indicates monoamine oxidase inhibitory.

### Table 2. Logistic Regression Analysis of Variables Related to Aortic Regurgitation and FDA Grade Regurgitation

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### Table 3. Interobserver Variability: Echo Readers

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<td>11.2</td>
</tr>
<tr>
<td></td>
<td>Aortic valve sclerosis</td>
<td>87.9</td>
<td>9.5</td>
</tr>
</tbody>
</table>

Total n=412. $\kappa$ indicates weighted $\kappa$ value.
though most subjects were middle-aged (Table 2). A significant effect of age was limited to the control subjects, however, which suggests the lack of any interaction between age and dexfenfluramine treatment.

In contrast, evidence was found of an interactive effect of diastolic blood pressure at the time of the echocardiogram and dexfenfluramine on the prevalence of aortic regurgitation. No relationship between diastolic blood pressure and aortic regurgitation was observed in controls. This suggests that a valve already exposed to dexfenfluramine is more likely to exhibit regurgitation when subjected to a higher pressure gradient. The high percentage of regurgitation in patients with diastolic pressure > 95 mm Hg (46.7%), not observed in controls, raises the possibility that the regurgitation prevalences reported here may underestimate the number of valves affected by dexfenfluramine. Of note, no relationship existed between a history of hypertension and valve regurgitation in the present study.

Although the mechanism of valvulopathy associated with anorexigen remains speculative, a role for serotonin has been suggested.1,16 Serotonin levels in plasma are limited by platelet uptake and circulating monoamine oxidase.12 Any increase in serotonin levels in platelets or plasma due to fenfluramine or dexfenfluramine might be potentiated by drugs possessing monoamine oxidase inhibitory activity, such as phentermine. Phentermine exposure was an exclusion in the present study, but a list of other medications with documented monoamine oxidase inhibitory activity was assembled (Appendix A). A trend was observed toward more frequent FDA-grade regurgitation in dexfenfluramine patients also taking ≥1 of these medications.

Limitations
The size and design of the present study yield a 90% power to detect an ≈10% difference between regurgitation prevalences in 2 groups; thus, small differences could be missed. The absence of significant differences between dexfenfluramine patients and controls in the prevalence of mitral regurgitation may reflect this limitation. A longitudinal study design, rather than the cross-sectional design used here, is preferable for examining the questions of whether dexfenfluramine causes valve disease and whether regression occurs.

In the present study, analyses of factors that influence the prevalence of valve regurgitation in addition to dexfenfluramine were not prespecified in the study design. Two of these factors resulted in only statistical trends: echocardiogram quality and concomitant treatment with drugs that show monoamine oxidase inhibitory activity. Thus, these results should be considered preliminary, pending study of a larger number of dexfenfluramine patients.

Conclusions
The hypothesis that the use of dexfenfluramine is associated with potentially clinically significant valve regurgitation is supported by the present study. The prevalence of abnormal valve regurgitation attributable to dexfenfluramine (the difference between treated patients and controls) when evaluated 8.5 months after discontinuation of therapy is estimated to be 5.5%. These data also indicate that factors in addition to dexfenfluramine are independently associated with significant valve regurgitation in obese patients. Variations in the prevalence of these factors may contribute to differences between the present study and others and may warrant consideration in the design and analysis of further work in this area. Furthermore, the decline in the frequency of regurgitation over time after drug discontinuation may indicate the potential for regression of valvulopathy associated with dexfenfluramine.

Appendix A
Monoamine Oxidase–Inhibitory Medications
Medications classified as possessing potentially significant monoamine oxidase–inhibitory activity (references available on request) are as follows: amiloride, benzphetamine, betahistine, chlorpromazine, clonidine, estrogens, maprotiline, promethazine, ranitidine, St John’s wort, l-thyroxine, verapamil, and viloxazine.

Appendix B
Study Investigators
The investigators of the present study were C. John Baumgartner, MD, Robert Ketroser, MD, Edina, MN, Bruce W. Bode, MD, and Steven Rosenthal, MD, Atlanta, Ga; Paul S. Bradley, MD, and Robert Rollings, MD, Savannah, Ga; Michael J. Brennan, MD, and Michael Gordon, MD, Phoenix, Az; Robert S. Busch, MD, and David L. Putnam, MD, Albany, NY; Stephen E. Dippe, MD, and Scott Robinson, MD, Scottsdale, Az; P. Barton Duell, MD, and George Panteley, MD, Portland, Or; Ronald J. Graf, MD, and Timothy Chang, MD, Tacoma, Wash; John H. Gray, DO, and Charles Valone, DO, Lorain, Ohio; Robert W. Harrison III, MD, and Karl Schwarz, MD, Rochester, NY; Lawrence J. Kessel, MD, and Morris Kotler, MD, Philadelphia, Pa; Charles Kilo, MD, and Bassam Aljounidi, MD, St Louis, Mo; Edward M. Kowaloff, MD, Thomas Najarian, MD, Eric S. Schreiber, MD, and Judy Mangione, MD, Cambridge, Mass; Lester S. Kritzer, MD, and Hazar Dahan, MD, Manchester, Conn; Paul C. Lee, MD, and Tom Sbarra, MD, E Falmouth, Mass; Sam Lerman, MD, and Howard Berlin, MD, Hollywood, Fla; Kathryn Jean Lucas, MD, and Robert Hoff, MD, Atlanta, Ga; John A. Merenich, MD, and Steve Friedrich, MD, Aurora, Co; Laurance B. Nilsen, MD, and Michael Gordon, MD, Phoenix, Az; Beverley E. Phillipson, MD, and Mark Hart, MD, Portland, Or; John Sheehan, MD, Daniel Weiss, MD, and Joel Holland, MD, Cleveland, Ohio; Barbara A. Smith, MD, and Donna Nash, RN, Anaheim, Calif; John M. Tsao, MD, and Bruce Jackson, MD, Torrance, Calif; and Chandrasekhar Varma, MD, and Douglas Moir, MD, Escondido, Calif.

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